

multi-center, randomized, double-blind study involving 4,360 drug-naïve patients recently diagnosed with type 2 diabetes (less than 3 years). Participants were randomized to rosiglitazone (Avandia®), metformin and glyburide. Participants were followed for four to six years to

metformin) and weight gain (6.9% Avandia, 3.3% glyburide and 1.2% metformin). The risk of edema and weight gain for patients taking Avandia were already well known as these adverse events have appeared in other studies. However, during ADOPT, a new event appeared that

Efficacy in Drug-Naïve Diabetic Patients). SERENADE was a multi-center, randomized, double-blind, placebo-controlled, parallel-group study comparing rimonabant (Acomplia®) to placebo in improving blood sugar control in the treatment-naïve type 2 patients not ade-

Which of these drugs will rule the type 2 market?



examine the long-term efficacy of each drug used as initial monotherapy on blood sugar control, insulin resistance and beta-cell function.

The trial showed that patients treated with Avandia reduced the risk of monotherapy failure by 32% compared to metformin and 63% compared to glyburide at five years. These are encouraging results until one examines the adverse event profile of the various drugs. After the five-year study, the most common adverse events were edema (Avandia 14.1%, 8.5% glyburide and 7.2%

was previously unknown.

During ADOPT, 9.3% of the women taking Avandia reported a higher fracture rate, most commonly foot and upper limb. This event did not appear in men and the company was at somewhat of a loss trying to explain the appearance of this new adverse event. They would only state this issue warrants further study.

Also released at the IDF conference from Sanofi-Aventis (NYSE:SNY) were results from SERENADE (Study Evaluating Rimonabant

quately controlled by diet alone for a period of six months.

Originally targeted as a treatment for obesity, Sanofi also believed Acomplia could be used as a treatment for type 2 diabetes. While the results of the study did show Acomplia did a fine job of lowering A1C and producing weight loss, not all the news was positive. The fact that nearly 10% of the study participants dropped out of the study is cause for concern.

The main concern surrounding Acomplia since its introduction has been the possibility of psychiatric disorders. In this study, 17.4% of the patients taking Acomplia experienced some type of psychiatric event, which were defined as anxiety, depressed mood, insomnia, depression and initial insomnia.

While Merck (NYSE:MRK) did not present any findings at the IDF, their new DPP-4 Januvia is off to a strong start. The main selling point for Januvia isn't that it produces better outcomes than Avandia or Actos, a TZD marketed by Lilly (NYSE:LLY) and made by Takeda; it is that it produces comparable outcomes with fewer adverse events. In reality, Januvia used as monotherapy is actually inferior to metformin; only when used in conjunction with metformin are there any meaningful reductions in A1C.

Although there does not appear to be any significant adverse events for patients using Januvia, there are concerns that long term usage of the drug may lead to an increase in cancer cells. According to a study published this past July in ScienceDirect, DPP-4 inhibitors extend GLP-2 mediated tumour promoting effects on intestinal cancer cells by K. Masur, F Schwartz, F. Entschladen, B. Niggemann, K.S. Zaenker; "Considering elevated GLP-2 levels due to treatment with DPP-4 inhibitors, a higher proliferation rate will be an advantage for all cells with respect to tumour progression. Additionally, cell lines with metastatic potential will be more active in cell migration, even when GLP-2 itself does not induce metastasis. Furthermore, if there is a trend in down-regulating CD26/DPP-4 activi-

Besides facing a variety of issues, all of these oral medications are up against one indisputable fact; they face an uphill battle in upsetting the current king of the hill in treating type 2 diabetes - metformin. Almost 50 years after it was first launched, metformin remains entrenched in the physicians' mind as the drug of choice to treat their type 2 patients. This is not to say that metformin is free from adverse events, the most common being gastrointestinal. What metformin has that everyone lacks is its proven ability to lower A1C, long track record of patient usage and the fact that it's available as generic. The fact of the matter is the real battle in the type 2 oral market is deciding which drug physicians will choose to complement metformin.



ty in cancer cells per se, the use of DPP-4 inhibitors to treat diseases like diabetes, short bowel syndrome or ulcerative colitis, where a long time treatment is indispensable, would amplify those tumour promoting effects."

Concerns have already been raised with Galvus, a DPP-4 from Novartis (NYSE:NVS) and Saxagliptin, a DPP-4 from Bristol-Myers Squibb (NYSE:BMJ) over skin lesions. For their part, Merck insists that this skin lesion issue is unique to their competitors and not an issue with the DPP-4 class as a whole.

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In an editorial that appeared in the December 7th issue of the New England Journal of Medicine by Dr. David M. Nathan, entitled Thiazolidinediones for Initial Treatment of Type 2 Diabetes?, which came out in response to the ADOPT results and summed up how the majority of physicians see metformin. Commenting on the ADOPT

results Dr. Nathan wrote, “The authors conclude that the “relative costs of these medications, their profiles of adverse events, and their potential risk and benefits” should be considered in choosing among them. Given the modest glycemic benefit of rosiglitazone (with the risk of fluid retention and weight gain) and higher cost (including the need for more statins and diuretics), metformin remains the logical choice when initiating pharmacotherapy for type 2 diabetes.”

Some will point to the fact that combination therapy is becoming the standard for treating type 2 diabetes and that combination therapy should be introduced earlier into the treatment regimen. With nearly 70% of type 2 patients failing to achieve good control and a growing body of research showing the effectiveness of combination therapy, there is a strong basis for this feeling.

However, unlike metformin, the more that is learned about TZDs and DPP-4s, the more concerns physicians have to consider. It’s easy to see why there is physician resistance in moving past metformin as a stand alone treatment for type 2 diabetes.

Watching all this are the people at Amylin (NASDAQ:AMLN), the makers of Byetta. Although Byetta is an injectable drug, physicians have fallen in love with Byetta as it produces solid A1C lowering, progressive weight loss and simplicity of administration. This is one reason Byetta sales had been accelerating until the launch of Januvia. It should be noted that physicians are not taking existing patients off Byetta and replacing it with Januvia. The reason for the slower prescription growth is that physicians are experimenting

with Januvia for patients who typically would move from orals alone to orals plus Byetta.

This is not unlike what happened when Byetta first came out, when physicians tried the drug on a select group of patients and waited to hear

Already, the major players - Roche, LifeScan (a unit of Johnson and Johnson (NYSE:JNJ), Bayer (NYSE:BAY) and Abbott (NYSE:ABT) are feeling the heat. With the market growing at less than 10% annually, prices coming down and the prospect of competitive bidding on the horizon, these companies are already taking steps to lower cost. In 2007, look for the BGM companies to follow the path set by the major pharmaceutical companies by slashing their sales forces.

back before prescribing the drug to a wider section of their patient population. Unlike Byetta, the early reports on Januvia have not been encouraging. Diabetic Investor suspects that after the hype over Januvia subsides, Byetta prescriptions, in particular new patient starts, will once again accelerate.

Of more concern to Amylin are the strange actions of their partner with Byetta, Eli Lilly. During their annual investment community update on December 7th, Lilly appeared to be talking out of both sides of their mouth when it came to Amylin. At some points during the presentation, Lilly lavished praise on Amylin and the strong performance of Byetta. At other times, the company seemed to cast some doubt over the future of

Amylin’s next product, the long-acting once-a-week version of Byetta, known as Byetta LAR. Given the challenges Lilly faces in the diabetes franchise and the mega-blockbuster potential of Byetta LAR, the company’s comments are even more confusing.

Diabetic Investor has long wondered why Lilly hasn’t taken the next step with Amylin by buying the company before Byetta LAR hits the market. With their insulin franchise now third behind Novo Nordisk (NYSE:NVO) and Sanofi-Aventis, Actos under pressure from Januvia, and a weak pipeline of diabetes products, acquiring Amylin seems to make sense to everyone but Lilly. Lilly could be in for a rude awakening should another company come along who sees the long term picture with Amylin and steals the company while its shares are under pressure.

A group of companies that should be rejoicing over the growing attention being given to the type 2 market are all the companies in the blood glucose monitoring market (BGM). It would seem that although type 2 patients do not check their glucose levels as often as insulin using patients, all this attention to type 2 patients would drive companies in the oral medication market to use glucose monitoring as a means for product validation. While A1C may be the gold standard for measuring control, this is not a test that is easily performed by the patient. There are also a host of studies that show that patients who monitor their glucose levels on a regular basis achieve better control of their diabetes. Finally, the sheer size of the market should

drive these companies - there are nearly 17 million non-insulin patients in America alone.

Yet BGM companies are singing the blues as the market forces and their own failures have made conditions in the BGM market the toughest they've been in years. Instead of trying to expand the market beyond insulin using patients who account for the majority of test strips used, BGM companies are in fierce competition for market share in this finite market segment. Making matters worse is the perception that patients with type 2 diabetes should not be checking their glucose values on a regular basis.

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Diabetic Investor doesn't see a much brighter future for the continuous glucose monitoring (CGM) market either and 2007 could be a watershed year for this segment of the market. While everyone is concentrating on whether or not CGM systems will receive reimbursement, they are missing the real story here. Even with reimbursement, something Diabetic Investor does not see coming anytime soon, if at all, no CGM company will be commercially successful if patients don't use sensors

Diabetic Investor sees 2007 shaping up as a difficult year for the diabetes market as a whole. The epidemic growth rate of the disease has brought new players into the market at a time when pricing pressure has intensified. Physicians will be overwhelmed with study data as drug companies try to position their offerings as the best alternative to metformin. With the notable exception of Insulet, device companies will be slashing their sales staff in a desperate attempt to control costs. By the time 2007 is over, it could well go down as the year the diabetes market made it into the big time. As one of the few growth areas for drug and device companies, the diabetes market is in the midst of major changes. The stakes are high and the competition will be intense. Diabetic Investor is looking forward to seeing who comes out on top. An interesting year ahead!!!!

on a regular basis. This market segment was not built around the idea that patients would use the device on an intermittent basis; CGM was built around the same principal as BGM; namely, that patients would use the system each and every day.

What we are learning from patients who use CGM systems is that after building a database of information, there is little need to use the device on a daily basis. Even if the system was fully reimbursed, this issue won't go away. What this means is for CGM companies to grow revenue, they must constantly add new patients. Looked at realistically, the market just isn't big enough to support the sales estimates many have for the CGM market.

Facing a similar problem is the insulin pump market. For years, Diabetic Investor has stated that the insulin pump market is not large enough or growing fast enough to support all the current and many future players getting set to enter the market. This will not change in 2007; what will change in 2007 is who will take the number two spot behind market leader Medtronic (NYSE:MDT). Look for Insulet, the makers of the OmniPod, to overtake Smiths Medical and Animas, and vault to the number two spot in terms of market share. Insulet will take full advantage of their new position by going public sometime in the first half of 2007.

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